

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Original) A non-human transgenic mammal whose genome comprises:

i) a first transgene comprising a mammary gland specific transcriptional control region operably linked to cDNA encoding a rotavirus protein selected from VP2, VP4, VP6 and VP7 and wherein said cDNA comprises a secretion signal sequence;

ii) at least a second transgene comprising a mammary gland specific transcriptional control region operably linked to cDNA encoding another rotavirus protein selected from VP2, VP4, VP6 and VP7;

wherein said cDNA comprises a secretion signal sequence, which cDNA sequence is wild type or modified;

said modification being selected from glycosylation sites elimination by Asp->Gln substitution, combined Glycosylation by Asp->Gln substitution/splicing site mutation, combined glycosylation by Asp->Gln substitution/splicing site mutation and codon optimization, codon optimization, elimination of premature polyadenylation sites, and point mutation and combination thereof;

and wherein said rotavirus proteins are secreted separately and auto-assembled in milk in rotavirus like particles (VLP) or aggregates of said rotavirus proteins.

2. (Original) The non-human transgenic mammal according to claim 1, wherein the first transgene comprises a wild type or modified cDNA encoding a VP2 rotavirus protein and the second transgene comprises a wild type or modified cDNA encoding a VP6 rotavirus protein.

3. (Original) The non-human transgenic mammal according to claim 2, further comprising a third or fourth transgene comprising a cDNA encoding a rotavirus protein selected from VP4 and VP7.

4. (Currently amended) The non-human transgenic mammal according to ~~one of claims 1 to 3~~ claim 1, wherein at least one of the cDNAs encoding VP2, VP4, VP6 and VP7 comprises at least one modification chosen from glycosylation sites elimination by Asp->Gln substitution, combined glycosylation by Asp->Gln substitution/splicing site mutation, combined glycosylation by Asp->Gln substitution/splicing site mutation and codon optimization, codon optimization, elimination of premature polyadenylation sites, and point mutation, wherein said modification enhance the mRNA translation of said proteins in mammary gland.

5. (Currently amended) The non-human transgenic mammal according to ~~claim 1 or 4~~ claim 1, wherein the cDNA encoding VP2 is selected from SEQ ID No 1 to 6.

6. (Currently amended) The non-human transgenic mammal according to ~~claim 1 or 4~~ claim 1, wherein the cDNA encoding VP6 is selected from SEQ ID No 10 to 16.

7. (Currently amended) The non-human transgenic mammal according to ~~claim 1 or 4~~ claim 1, wherein the first transgene is a modified cDNA encoding VP2.

8. (Currently amended) The non-human transgenic mammal according to ~~claim 9~~ claim 1, wherein the second transgene is a native or modified cDNA encoding VP4, VP6 or VP7, preferably VP6.

9. (Currently amended) The non-human transgenic mammal according to ~~claim 1 or 4~~ claim 1, wherein the cDNA encoding VP4 is selected from SEQ ID No 7 to 9.

10. (Currently amended) The non-human transgenic mammal according to ~~claim 1 or 4~~ claim 1, wherein the cDNA encoding VP7 is selected from SEQ ID No 17 to 21.

11. (Currently amended) The non-human transgenic mammal according to ~~one of claims 1 to 8~~ claim 1, wherein said VP2 and VP6 assemble in VLP or aggregates of at least 5000 KDA.

12. (Currently amended) The non-human transgenic mammal according to ~~one of claims 1 to 8~~ claim 1, wherein the milk contains at least 10 pg/ml, preferably at least 100, ug/ml of both VP2 and VP6.

13. (Currently amended) The non-human transgenic mammal according to ~~one of~~ ~~claims 1 to 12~~ claim 1, wherein said mammary gland specific transcriptional control region is selected from a milk serum protein or a casein protein, in particular the WAP promoter such as the long mouse or rabbit WAP promoter.

14. (Original) The non-human transgenic mammal according to claim 13, wherein said mammary gland specific transcriptional control region is the long WAP rabbit promoter, such as a region of at least 3 kb, 3 kb to 6.3 kb or at least 6.3 kb from the translation initiation start of the rabbit WAP promoter.

15. (Currently amended) The non-human transgenic mammal according to ~~one of~~ ~~claims 1 to 14~~ claim 1, wherein the transgene further comprises the genomic sequences surrounding the WAP gene, preferably at least 140Kb upstream and at least 10Kb downstream of the WAP gene from sheep, pig, goat, cow, rabbit, rat or mouse.

16. (Currently amended) The non-human transgenic mammal according to ~~one of~~ ~~claims 1 to 15~~ claim 1, wherein the transgene further comprises the 5'HS4 region from the chicken β -globin gene cluster.

17. (Currently amended) The non-human transgenic mammal according to ~~one of~~ ~~claims 1 to 16~~ claim 1, wherein the transgene further comprises one or several introns, such as introns of SV40 early genes, SV40 late genes, β -globin genes, EFla gene, as 1-casein gene, rabbit WAP gene, bovine and human growth hormone genes.

18. (Currently amended) The non-human transgenic mammal according to ~~one of~~ ~~claims 1 to 17~~ claim 1, wherein the transgene further comprises one or several enhancers located in the promoter region and/or in the transcribed region, such as enhancers of the asl-casein gene (in monomer or multimer), LTR from HTLV1 genome, immunoglobulin gene, LTR from MMTV genome, distal upstream regions (up to 140 kb) of the WAP genes and p-globin gene.

19. (Currently amended) The non-human transgenic mammal according to ~~one of~~ ~~claims 1 to 18~~ claim 1, wherein the transgene further comprises one or several transcription

terminators, such as terminators of the SV40 early and late genes, P-globin genes, WAP gene, and bovine and human growth hormone.

20. (Currently amended) The non-human transgenic mammal according to ~~one of claims 1 to 19~~ claim 1, wherein at least two cDNAs encoding a rotavirus protein selected from VP2, VP4, VP6 and VP7 are within one single said transgene.

21. (Currently amended) The non-human transgenic mammal according to ~~one of claims 1 to 20~~ claim 1, wherein the transgene further comprises a coding sequence for an exogenous or endogenous peptide or protein or epitope thereof and wherein non-human transgenic mammal produce recombinant VLP harboring epitopes in the milk.

22. (Original) The non-human transgenic mammal according to claim 21, wherein said epitope is a HIV epitope, in particular RTPKIQV (SEQ ID No 22) or ELDKWA (SEQ ID No 23) or both.

23. (Currently amended) The non-human transgenic mammal according to ~~one of claims 1 to 22~~ claim 1, said mammal being a sheep, pig, goat, cow, rabbit, rat or mouse.

24. (Currently amended) A method for producing a recombinant rotavirus VLP or protein parts of VLP comprising the steps of : (a) inserting into a non-human mammalian embryo or fertilized egg a transgene as defined in ~~one of claims 1 to 10 and 15 to 22~~ claim 1, (b) allowing said embryo or fertilized egg to develop into an adult mammal, (c) inducing lactation in said non-human mammal, or in a female descendant of said non-human mammal in which said transgene is present in the mammary tissue genome, (d) collecting milk of said lactating non-human mammal, and (e) isolating said VLP or protein parts of VLP from said collected milk.

25. (Currently amended) A method for producing a recombinant rotavirus VLP or protein parts of VLP comprising the steps of : (a) inducing lactation in a transgenic non-human mammal according to ~~one of claims 1 to 23~~ claim 1, or in a female descendant of said non-human mammal, (b) collecting milk of said lactating non-human mammal, and (c) isolating said VLP or protein parts of VLP from said collected milk.

26. (Original) The method according to claim 25, wherein protein parts of VLP comprise trimers of VP6.

27. (Currently amended) The method according to ~~one of claims 25 to 26~~ claim 25, wherein VP2 and VP6 present in milk are not degraded, not cleaved and not glycosylated.

28. (Currently amended) The method according to ~~claim 25 to 27~~ claim 25, wherein said protein parts of VLP are purified, eventually dissociated, and brought into contact in conditions to reassemble recombinant VLP.

29. (Currently amended) The method according to ~~one of claims 25 to 28~~ claim 25, wherein the purification comprises a first step consisting of preparing lactoserum.

30. (Currently amended) ~~The use of a recombinant epitope harboring VLP obtained from a non human transgenic animal according to one of claims 1 to 24 or the method as defined in one of claims 25 to 29~~ A method for the manufacture of an immunogenic composition, such as a vaccine, for treating or preventing infection with parasites, bacteria or virus, including HIV, papilloma, herpes, hepatitis A, B or C, RSV, coronavirus, foot and mouth disease, rotavirus, Aujeszki disease, Marek disease, comprising obtaining a recombinant epitope harboring VLP from a non human transgenic animal according to claim 25.

31. (Currently amended) ~~The use of recombinant epitope harboring VLP obtained from a non human transgenic animal according to one of claims 1 to 24 or the method as defined in one of claims 25 to 29~~ A method for the manufacture of an immunogenic composition, such as a vaccine, for treating or preventing cancer, auto-immune diseases and metabolic disorders, comprising obtaining a recombinant epitope harboring VLP from a non human transgenic animal according to claim 25.

32. (Currently amended) ~~The use according to one of claims 30 to 31, wherein said~~ A method of adapting a medicament as claimed in claim 30 is adapted for oral, rectal administration or intravenous, intramuscular, subcutaneous injection.

33. (Currently amended) A method of making a A pharmaceutical composition comprising a recombinant epitope harboring VLP obtained from a non human transgenic animal according to ~~one of claims 1 to 24 or the method as defined in one of claims 25 to 29~~ claim 25 suitable for a rectal administration, which composition is an injectable solution or a suppository.